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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED, and TAKEDA PHARMACEUTICALS U.S.A., INC.	)
Plaintiffs,	) C.A. No. 20-cv-8966-SRC-CLW
v.	)
NORWICH PHARMACEUTICALS, INC.	)
Defendant.	)

TAKEDA'S OPENING CLAIM CONSTRUCTION BRIEF

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I. Introduction

Plaintiffs Takeda Pharmaceutical Co. Ltd. and Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") hereby submit their Opening Claim Construction Brief in support of their proposed claim constructions for the six categories of disputed claim terms of the eighteen patents-in-suit (Exs. 1-18)[1] in this Hatch-Waxman case. These same patents were previously litigated before this Court (the "Prior Litigation" (C.A. No. 11-3781-SRC)). In the Prior Litigation, this Court granted the Shire plaintiffs summary judgment of infringement and of no invalidity of eighteen claims. *Shire LLC v. Amneal Pharms., LLC,* No. 11-3781-SRC, 2014 WL 2861430 (D.N.J. June 23, 2014), *aff'd in relevant part*, 802 F.3d 1301 (Fed. Cir. 2015). Since then, Takeda acquired Shire and Vyvanse®. This Court held a claim construction hearing and entered a claim construction order in the Prior Litigation. *Shire LLC et al. v. Amneal Pharm., LLC*, No. 11-3781-SRC, 2013 WL 4045622 (D.N.J. Aug. 8, 2013). Takeda's constructions generally adhere to the Court's prior constructions or to constructions that all parties agreed to in the Prior Litigation.

The parties dispute six categories of claim terms. ***First***, with respect to the term "L-lysine-d-amphetamine mesylate" (and variations of the same), Takeda proposes that the terms "L-lysine-d-amphetamine" and "mesylate" should be understood together, as they arise in the claims and as taught by the specification. Norwich improperly seeks to construe the terms independently of each other. ***Second***, the parties dispute the construction of the term "limited bioavailability of amphetamine when administered through alternative routes of administration." Takeda's construction clarifies the comparator by which to gauge the "limited bioavailability." Norwich declines to offer a competing construction and simply relies on the unspecified "plain and ordinary meaning." ***Third***, regarding the construction of "C_{max} which results in euphoria," the parties agree

[1] "Ex. __" refers to Exhibits to the *Declaration of Andrew S. Roper, Esq.* dated July 27, 2021.

that the term should be construed according to its plain and ordinary meaning. However, Norwich refuses to agree with Takeda's construction that clarifies the plain and ordinary meaning of "euphoria" as a feeling of well-being. Of note, Norwich does not provide a competing interpretation of the term. ***Fourth***, Takeda seeks to construe the term "amphetamine" on a claim-by-claim basis. In some instances, the term refers specifically to "d-amphetamine" (such as that released from L-lysine-d-amphetamine); in others, the term broadly refers to "the genus of amphetamines." By contrast, Norwich advances a broad construction in all contexts. ***Fifth***, the parties dispute the construction of the term "isolated." Norwich's construction seeks to carve out its dimesylate salt ANDA product from the scope of the claims, but is unsupported by the intrinsic evidence. ***Sixth***, the parties dispute the construction of claims reciting certain "milligram" amounts. Although the parties agree that the terms should be understood according to their plain and ordinary meaning (as decided by the Court in the Prior Litigation), Norwich improperly injects the word "precisely" into its proposed construction.

Takeda's constructions also accord with well-established principles of claim construction. In particular, Takeda's constructions are supported by the intrinsic evidence and the context of the claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). In addition, Takeda's constructions are supported by extrinsic evidence, including the declarations of its experts Leonard J. Chyall, Ph.D. (an organic and analytical chemistry expert) and David Taft, Ph.D. (a pharmacokinetics expert) regarding the skill level of a **p**erson of **o**rdinary **s**kill in the **a**rt ("POSA") and how such a POSA would understand the disputed claim terms.[2] Accordingly, Takeda respectfully requests that the Court adopt all of its proposed constructions in their entirety.

[2] The declarations of Dr. Leonard J. Chyall and Dr. David R. Taft are cited herein as "Chyall ¶ __" and "Taft ¶ __", respectively.

II. Background

Takeda is asserting that Norwich infringes the patents-in-suit by virtue of its generic versions of Takeda's drug Vyvanse® (lisdexamfetamine dimesylate), which is indicated for Attention Deficit Hyperactivity Disorder ("ADHD") and Binge Eating Disorder ("BED").

Vyvanse® addresses problems associated with abuse of existing central nervous system stimulants such as amphetamine drugs. "Because of their stimulating effects, amphetamines, including amphetamine derivatives and analogs, are subject to abuse." (*See*, *e.g.*, Ex. 15, '561 patent, col.1 ll.49–51). Even when amphetamine drugs are prescribed for therapeutic purposes, they may be used in a manner inconsistent with the manufacturer's instructions, e.g., "it is possible for individuals to inappropriately self-administer higher than prescribed quantities of the drug or to alter either the product or the route of administration (e.g., inhalation (snorting), injection, and smoking)." (*See, e.g.*, Ex. 15, '561 patent, col.1 ll.57–61; *see also id.* col.10 ll.20– 25). Such abuse may allow an individual to obtain a "high." (*See* Ex. 15, '561 patent, col.1 ll.63–65).

The patents-in-suit relate to L-lysine-d-amphetamine (lisdexamfetamine), which is an inactive prodrug of d-amphetamine. Following dosing of the claimed L-lysine-d-amphetamine compositions, the pharmacologically active d-amphetamine may be gradually released from L-lysine-d-amphetamine. (Taft ¶ 27; Ex. 2, '735 patent, col.1 ll.25–28; Ex. 33, TAKVYV01724997 at 1731577, '561 patent file history). The steady release of d-amphetamine from the claimed L-lysine-d-amphetamine compositions into systemic circulation provides a long duration of effect throughout the day. (*See, e.g.*, Ex. 15, '561 patent, Examples 33–35 (TAKVYV01701599-604)). Additionally, the claimed L-lysine-d-amphetamine compositions may prevent the rapid increase or "spiking" of d-amphetamine blood serum concentrations and associated euphoria sought by drug abusers. (*See, e.g.*, Ex. 15, '561 patent, col. 11 ll. 22-26). The claimed L-lysine-d-amphetamine compositions may also exhibit limited bioavailability as compared to other d-

amphetamine products when administered via alternative routes of administration that are often employed in illicit use (e.g., snorting). (*See, e.g.*, Ex. 2, '735 patent, col.1 ll.33–36, col.9 ll.11–15, Table 46). In short, the claimed L-lysine-d-amphetamine compositions may have reduced abuse potential. (*See, e.g.*, Ex. 15, '561 patent, Examples 36–37).

III. General Claim Construction Principles and the Level of Ordinary Skill in the Art

Claim terms "are generally given their ordinary and customary meaning," i.e., that which they "would have to a [POSA] in question at the time of the invention." *Phillips*, 415 F.3d at 1312–13. A court considers several factors in formulating the "hypothetical" POSA, including the: "type of problems encountered in [the] art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962–63 (Fed. Cir. 1986).

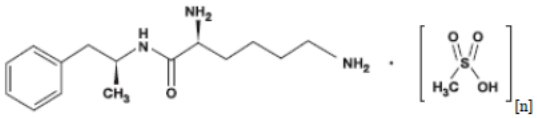
Takeda's experts opined that a POSA is "a person with an academic degree of Doctor of Philosophy (or equivalent degree) in a field related to pharmaceutical sciences with approximately 1 year of relevant experience or a person with commensurate experience." (ECF No. 77 at 7; Chyall ¶ 27; Taft ¶ 24). While Norwich has offered a different definition, Takeda's claim construction positions do not change depending on which definition is used. (ECF No. 77 at 7; Chyall ¶ 28; Taft ¶ 26).

The ordinary meaning of a claim term may be derived from "a variety of sources," including both intrinsic and extrinsic to the patents-in-suit. *See Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1324–25 (Fed. Cir. 2002). "[T]he intrinsic evidence and particularly the claim language are the primary resources" for claim construction. *Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1348 (Fed. Cir. 2009). The claims, however, "must be read in view of the specification, of which they are a part." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979

(Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). The Federal Circuit has designated the specification "the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Additionally, courts may consider "the complete record of the proceedings before the PTO"—i.e., the prosecution history—to elucidate the meaning of a disputed claim term. *Phillips*, 415 F.3d at 1317. Extrinsic evidence such as dictionaries, treatises, and expert testimony may also be helpful in construing patent claims, but must always be "considered in the context of the intrinsic evidence." *Id.* at 1317–19.

IV. The Court Should Adopt Takeda's Constructions of the Disputed Claim Terms

A. Term 1: "Mesylate" Should Be Construed in the Context of "L-lysine-d-amphetamine"

Term	*Takeda's Construction*	*Norwich's Construction*
"L-lysine-d-amphetamine mesylate" or "mesylate salt of L-lysine-d-amphetamine" or "… wherein said salt is a mesylate salt."	a salt of L-lysine-d-amphetamine containing at least one CH3SO3- anion, which can be obtained from methanesulfonic acid (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide methanesulfonate 	"mesylate" / "a mesylate salt" means "a salt with any number of mesylate ions associated with it." No further construction required other than the construction of "L-lysine-d-amphetamine" at term 3.

Term 1 concerns the phrases "L-lysine-d-amphetamine mesylate" or "mesylate salt of L-lysine-d-amphetamine" or "… wherein said salt is a mesylate salt." (ECF No. 77, Ex. A at 1). The parties' dispute appears to relate to the number of mesylate ions that may be associated with L-lysine-d-amphetamine to form a salt. Norwich proposes that the term contemplates "any number of mesylate ions," whereas Takeda's construction is informed by the chemical structure of L-lysine-d-amphetamine. Norwich's construction should be rejected because it is unmoored from the perspective of a POSA and the claims.

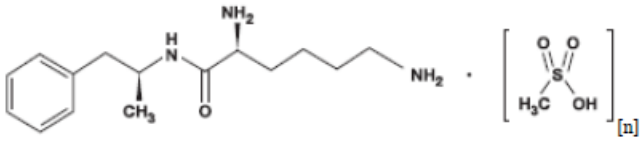
The intrinsic evidence supports Takeda's construction. Based on the claim language and the specification, a POSA would understand that term 1 encompasses not ***any*** mesylate salt, but a mesylate salt of L-lysine-d-amphetamine. (Chyall ¶¶ 30-52). For example, the affected claims recite "mesylate" only in relation to L-lysine-d-amphetamine:

> The composition of claim 1 or 2 wherein said L-lysine-d-amphetamine salt is L-lysine-d-amphetamine mesylate.

(Ex. 2, '735 patent at claim 3; *see also* ECF No. 77, Ex. A at 1-3 (listing claims encompassing term 1)). The specification supports the same conclusion. The specification explains that L-lysine-d-amphetamine can be described by the chemical name "2,6-diaminohexanoic acid-(1-methyl-2-phenylethyl)-amide." (*See, e.g.*, Ex. 7, '788 patent, col.18 ll.27-29). A POSA would have understood that this is synonymous with "(2*S*)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide," which is consistent with Takeda's construction. (Chyall ¶ 37). The specification further explains that (i) "[p]referably, the amphetamine is an amphetamine salt," (ii) "[p]harmaceutically acceptable salts . . . are known in the art," and (iii) "a preferred amphetamine salt is the mesylate salt (e.g., as in L-lysine-d-amphetamine-dimesylate)." (*See, e.g.*, Ex. 7, '788 patent, col.7 ll.28-56). Thus, a POSA would not separate the term "mesylate" from the context of the amphetamine compound (i.e., "L-lysine-d-amphetamine") in which it arises. (Chyall ¶¶ 40-41).

Additionally, as described in the specification, a POSA would understand that a mesylate salt of L-lysine-d-amphetamine "can be prepared by using methanesulfonic acid." (*See, e.g.*, Ex. 7, '788 patent, col.21 ll.4-6; *see also id.*, Example 2, Figure 2; Chyall ¶¶ 42-43)). Based on these disclosures, a POSA would have understood the term "mesylate" in accordance with its common understanding in the art, such that a mesylate salt of L-lysine-d-amphetamine is a salt of L-lysine-d-amphetamine containing at least one $CH_3SO_3^-$ anion, which can be obtained from

methanesulfonic acid. Synonymously, a POSA would understand term 1 as having the chemical name "(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide methanesulfonate" and structure:



This is consistent with Takeda's construction of the term. (ECF No. 77, Ex. A at 1).

A POSA would further understand that a mesylate salt of L-lysine-d-amphetamine must have at least one, but not more than two, mesylate (or CH_3SO_3-) anions associated with it. (Chyall ¶¶ 32-36, 43-52). Because L-lysine-d-amphetamine can have two sites on the molecule that can accept protons from acids to form salts, a POSA would expect that only these two sites are available for protonation. (Chyall ¶¶ 33-36, 47). This is consistent with the chemical structure set forth in the patents-in-suit (Ex. 4, '253 patent Figure 2 (TAKVYV01700293)), as well as the express construction of "L-lysine-d-amphetamine" and "L-lysine-d-amphetamine dimesylate" agreed to by the parties. (ECF No. 77 at 2-4; Chyall ¶¶ 44-46).

[redacted]

(Ex. 47, NPILDX_000000583 at 585 (red emphasis added)). [redacted]

[redacted] (Chyall ¶ 47).

By contrast, Norwich has declined to construe the term as proposed. Rather, Norwich offers a construction for a portion of the term (i.e., "mesylate") and states that "no further construction is required other than the [agreed-upon] construction of 'L-lysine-d-amphetamine' at term 3." (ECF No. 77 at 1).[3] But the claims do not recite the term "mesylate" in isolation—rather, the claims recite "mesylate" in the context of L-lysine-d-amphetamine. (Chyall ¶ 50). By divorcing the term "mesylate" from the context in which it appears, Norwich improperly attempts to broaden the scope of the claim to encompass a mesylate salt of L-lysine-d-amphetamine with "any number of mesylate ions associated with it." But "claim language must be construed in the context of the claim in which it appears. Extracting a single word from a claim divorced from the surrounding limitations can lead construction astray." *IGT v. Bally Gaming Int'l, Inc.*, 659 F.3d 1109, 1117 (Fed. Cir. 2011). Thus, a POSA would not understand the disputed terms to encompass salts of L-lysine-d-amphetamine having "any number" of mesylate ions associated with it, but only as many as L-lysine-d-amphetamine could accept (i.e., at least one, but not more than two).

Further, Norwich's construction yields an illogical result designed to intentionally broaden the claims to support its enablement and written description invalidity defenses. Norwich's construction refers to "a salt with ***any number*** of mesylate ions associated with it"—but Norwich does not specify what values are encompassed by the phrase "any number." In its broadest form, "any number" could refer to infinite values, including zero, and fractions of mesylate anions. (Chyall ¶ 52). A POSA would not understand term 1 to encompass a mesylate salt of L-lysine-d-amphetamine that might have, for example, 2/3 of a mesylate ion associated with it; such a construction is contrary to scientific principles. (Chyall ¶ 52). Because Norwich's construction is

[3] The parties have agreed to a construction of the terms "L-lysine-d-amphetamine" and "L-lysine-d-amphetamine dimesylate." (ECF No. 77 at 2-3).

unduly broad and results in an "illogical" and "ill-defined" claim scope, the Court should reject it. *Research Plastics, Inc. v. Federal Packaging Corp.*, 421 F.3d 1290, 1296 (Fed. Cir. 2005).

B. Term 4: "Limited Bioavailability of Amphetamine When Administered Through Alternative Routes of Administration" is a Comparison to D-Amphetamine Administered Through the Alternative Route

Term	*Takeda's Construction*	*Norwich's Construction*
"limited bioavailability of amphetamine when administered through alternative routes of administration"	"lower extent of absorption of the amphetamine released following administration of L-lysine-d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use compared to the extent of absorption of d-amphetamine following administration of a comparable molar dose of d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use."	No further construction required; plain and ordinary meaning

Takeda's construction clarifies that this term compares the "limited bioavailability" of the amphetamine released following administration of L-lysine-d-amphetamine or a salt thereof to d-amphetamine administered through the same alternative route of administration. (Taft ¶¶ 32-50). Norwich has not offered a competing construction in contravention of the Local Patent Rules. *See* L. Pat. R. 4.2(a) ("parties shall simultaneously exchange preliminary proposed constructions of each term identified by any party for claim construction, including constructions for each term for which 'plain and ordinary' meaning is asserted."). Nor has Norwich offered an expert to provide testimony on this issue. Norwich's refusal to clarify the plain and ordinary meaning of the term is improper and does not resolve the parties' dispute. "When the parties present a fundamental dispute regarding the scope of a claim term," the Court has a "duty to resolve it." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1362 (Fed. Cir. 2008). This Court should "reject[] . . . the notion that the disputed claim term[] require[s] no construction, or can be construed simply by reference, without explanation, to [its] 'plain and ordinary meaning.'" *See*

Baxter Healthcare Corp. v. Mylan Labs. Ltd., 346 F. Supp.3d 643, 653 (D.N.J. 2016). The Court should instead adopt Takeda's construction, which properly accounts for a comparator.

The specification makes clear that the proper comparator is d-amphetamine administered through alternative routes of administration. (*See, e.g.*, Ex. 2, '735 patent col. 9 ll. 12-15, col. 27 l. 60 – col. 28 l. 54, col. 30 l. 5 – col. 34 l. 34, col. 51 l. 4 – col. 52 l. 28; Taft ¶¶ 42-50). Examples 11-12, for instance, each depict a lower bioavailability of the amphetamine released following administration of L-lysine-d-amphetamine or a salt thereof as compared to the bioavailability of d-amphetamine.

Example 11

Decreased Intranasal Bioavailability of L-lysine-d-amphetamine vs. Amphetamine

Male Sprague-Dawley rats were dosed by intranasal administration with 3 mg/kg of amphetamine sulfate or L-lysine-d-amphetamine hydrochloride containing the equivalent amounts of d-amphetamine. L-lysine-d-amphetamine did not release any significant amount of d-amphetamine into circulation by IN administration. Mean (n=4) plasma amphetamine concentration curves of amphetamine vs. L-lysine-d-amphetamine are shown in FIG. **12**. Pharmacokinetic parameters for IN administration of L-lysine-d-amphetamine are summarized in Table 14.

TABLE 14

Pharmacokinetic Parameters of Amphetamine vs. L-lysine-d-amphetamine by IN Administration.

Drug	AUC (0–1.5 h) ng/ml h	Percent d-amphetamine	Cmax (ng/ml)	Percent d-amphetamine
Amphetamine	727	100	1,377	100
L-lysine-d-amphetamine	4	0.5	7	0.5

Example 11 illustrates that when lysine is conjugated to the active agent d-amphetamine the bioavailability by the intranasal route is substantially decreased thereby diminishing the ability to abuse the drug by this route.

Example 12

Intravenous Bioavailability of Amphetamine vs. L-lysine-d-amphetamine

Male Sprague-Dawley rats were dosed by intravenous tail vein injection with 1.5 mg/kg of d-amphetamine or L-lysine-d-amphetamine containing the equivalent amount of amphetamine. As observed with IN dosing, the conjugate did not release a significant amount of d-amphetamine. Mean (n=4) plasma concentration curves of amphetamine vs. L-lysine-d-amphetamine are shown in FIG. **13**. Pharmacokinetic parameters for IV administration of L-lysine-d-amphetamine are summarized in Table 15.

TABLE 15

Pharmacokinetic Parameters of d-amphetamine vs. L-lysine-d-amphetamine by IV Administration.

Drug	AUC (0–1.5 h) ng/ml h	% Amphetamine	Cmax (ng/ml)	% Amphetamine
Amphetamine	190	100	169	100
K-amphetamine	6	3	5	3

Example 12 illustrates that when lysine is conjugated to the active agent amphetamine the bioavailability of amphetamine by the intravenous route is substantially decreased, thereby diminishing the ability to abuse the drug by this route.

(Ex. 2, '735 patent Examples 11-12; Taft ¶¶ 43-47). Example 11 shows "Decreased Intranasal Bioavailability of L-lysine-d-amphetamine vs. Amphetamine" and "illustrates that when lysine is conjugated to the active agent d-amphetamine the bioavailability by the intranasal route is substantially decreased . . . ." (Ex. 2, '735 patent col. 27 l. 60 – col. 28 l. 23; Taft ¶¶ 44-45).

Similarly, Example 12 shows "Intravenous Bioavailability of Amphetamine v. L-lysine-d-amphetamine" and "illustrates that when lysine is conjugated to the active agent amphetamine the bioavailability of amphetamine by intravenous route is substantially decreased . . . ." (Ex. 2, '735 patent col. 28 ll. 25-54; Taft ¶¶ 46-47).

In these Examples, L-lysine-d-amphetamine has a lower extent of absorption of the amphetamine released following administration of L-lysine-d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use compared to the extent of absorption of d-amphetamine following administration of a comparable molar dose of d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use. (*See* Ex. 2, '735 patent col. 27 l. 60 – col. 28 l. 54; Taft ¶¶ 43-47, 50). Norwich's construction, or lack thereof, does not address the comparator. A POSA understands, based on the Examples presented in the specification, that d-amphetamine is the proper comparator. (*See* Taft ¶¶ 43-50). Because Takeda's construction accurately reflects a POSA's understanding of this term, the Court should adopt it.

The claims of a patent "must be read in view of the specification, of which they are a part." *Markman*, 52 F.3d at 979. Indeed, the specification is "the single best guide to the meaning of a disputed term," and usually is "dispositive." *Phillips*, 415 F.3d at 1315 (quoting *Vitronics*, 90 F.3d at 1582). This is especially so where, as here, the dispute concerns a technical term, because "the best source for understanding a technical term is the specification from which it arose . . . ." *See id.* And, as already explained, the specification (including the Examples therein) show that the "limited bioavailability" to which the claims refer requires comparison of the d-amphetamine, as released from L-lysine-d-amphetamine, to d-amphetamine itself. There is simply no other way to understand that term.

The patents-in-suit claim, for example, compositions comprising and methods of using L-lysine-d-amphetamine, or salts thereof. (*See, e.g.*, Ex. 2, '735 patent at claim 1; Taft ¶ 27). A POSA understands from the specification of the '735 patent that the compositions are, for example, "composition[s] for safely delivering amphetamine comprising a therapeutically effective amount of said amphetamine which has been covalently bound to a chemical moiety wherein said chemical moiety reduces the rate of absorption of the amphetamine as compared to the unbound amphetamine." (*See* Ex. 2, '735 patent col. 12 ll. 17-22; Taft ¶ 42). A POSA would read this disclosure and understand that a composition comprising L-lysine-d-amphetamine is, for example "for safely delivering [d-]amphetamine comprising a therapeutically effective amount of said [d-]amphetamine which has been covalently bound to [L-lysine] wherein said [L-lysine] reduces the rate of absorption of the [d-]amphetamine as compared to [d-amphetamine]." (Taft ¶ 42). Indeed, as the Applicants noted in prosecuting the patents-in-suit, "[t]he [] inventors [] discovered an amphetamine conjugate – L-lysine-d-amphetamine [], which can provide therapeutic amounts of d-amphetamine (AUC) upon oral administration, but without the high peak serum concentrations and rapid C_{max} observed with d-amphetamine." (*See, e.g.*, Ex. 24, TAKVYV01708704 at 1714902, '787 File History, Applicants May 12, 2009 Remarks at 3). The specification, together with the prosecution history of the patents-in-suit, provides ample support for Takeda's construction. Accordingly, the Court should adopt it.

C. Term 6: "C_{max} Which Results in Euphoria" Should Be Given Its Plain and Ordinary Meaning

Term	*Takeda's Construction*	*Norwich's Construction*
"C_{max} which results in euphoria"	Plain and ordinary meaning, i.e., "a C_{max} of the amphetamine released from L-lysine-d-amphetamine that results in euphoria (e.g., a feeling of well-being)"	No further construction; plain and ordinary meaning.

The parties agree that the term "C_{max} which results in euphoria" should be construed according to its plain and ordinary meaning. (Taft ¶¶ 51-62). The Court previously adopted the construction proffered by plaintiffs in the Prior Litigation. *Shire*, 2013 WL 4045622 at *16-17. The parties' constructions differ in that Takeda's construction clarifies the plain and ordinary meaning by incorporating the well-understood definition of "euphoria." (*See* ECF No. 77, Ex. A at 25). Norwich does not agree to Takeda's construction, but declines to provide further clarification as to what is meant by the plain and ordinary meaning of the term. (*Id.*; *see* L. Pat. R. 4.2(a)).

It is undisputed that a POSA would interpret the term "euphoria" according to its plain and ordinary meaning. (Taft ¶¶ 51-53, 57-62). Takeda's construction elaborates on the plain and ordinary meaning in a manner consistent with the intrinsic record. The specifications of the patents-in-suit explain: "In a preferred embodiment, no further sustained release additives are required to achieve a blunted or reduced pharmacokinetic curve (e.g., reduced euphoric effect) while achieving therapeutically effective amounts of amphetamine release when taken orally." (*E.g.*, Ex. 2, '735 patent, col.14 ll.36–40; Taft ¶ 60). A POSA would have understood that a blunted pharmacokinetic curve results in reduced euphoria—i.e., a reduced feeling of well-being—as compared to an immediate release pharmacokinetic curve. (Taft ¶ 60).

The file histories of the patents-in-suit also characterize euphoria as "undesirable." (*See* Ex. 24 TAKVYV01708704 at 1714902, '787 File History, Applicants May 12, 2009 Remarks at 3) ("The high peak serum concentrations observed with administration of d-amphetamine can result in an undesirable euphoric effect.")). A POSA would have understood that the pharmacokinetic properties of d-amphetamine result in a "feeling of well-being," and that this euphoric effect is "undesirable" because of its association with abuse. (Taft ¶ 61). The file

histories further support Takeda's construction. For example, the file histories describe an abuse liability study that explains the relationship between pharmacokinetics and euphoria with d-amphetamine. (Ex. 24 TAKVYV01708704 at 1714937-945, '787 File History). Thus, based on the intrinsic record, a POSA would have understood that a reduced euphoria—i.e., a reduced feeling of well-being—would be an objective of the invention. (Taft ¶ 59).

Additionally, Takeda's construction comports with extrinsic evidence. For example, Takeda's definition of "euphoria" is consistent with dictionary definitions of the term, which generally define euphoria as a state of "well-being." (*See* Ex. 38, TAKVYV01743255 at 257, Stedman's Medical Dictionary (26th ed. 1995) ("a feeling of well-being, commonly exaggerated and not necessarily well founded"); Ex. 39, TAKVYV01745277 at 280, The Dictionary of Medicine (3d ed. 2000) ("feeling of extreme happiness"); Ex. 44, TAKVYV01745282 at 285, Dictionary of Pharmacy (University of South Carolina Press 1986) ("an extreme state of perceived well-being"); Ex. 40, TAKVYV01745286 at 289, Merriam Webster's Medical Desk Dictionary (1996) ("feeling of well-being or elation"); and Ex. 41, TAKVYV01745290 at 293, Merriam Webster's Medical Dictionary (1995) ("feeling of well-being or elation")). Norwich has no basis to dispute the amply supported plain and ordinary meaning of the term, especially when it provides no construction.

Takeda provides a construction supported by the intrinsic record, expert testimony, and dictionary definitions. Because Norwich has failed to provide a competing construction or an expert witness to explain how a POSA would understand the term, its construction should be rejected. *See Baxter Healthcare*, 346 F. Supp.3d at 653; L. Pat. R. 4.2(a).

D. Term 9: A POSA Would Understand Construction of "Amphetamine" Depends on Context

"Amphetamine" Terms			
No.	*Term*	*Takeda's Construction*	*Norwich's Construction*
9	"amphetamine"	See infra, Joint Term Nos. 9(a)-9(g)	"any sympathomimetic phenethylamine derivative that has central nervous system stimulant activity"
9(a)	"compared to amphetamine alone"	"compared to the amphetamine released from L-lysine-d-amphetamine, namely d-amphetamine"	No further construction required other than "amphetamine" above
9(b), 9(d)	"compared to unbound amphetamine" *or* "unbound amphetamine"	"compared to the amphetamine portion of L-lysine-d-amphetamine when it is unbound, namely, d-amphetamine" *or* "the amphetamine portion of L-lysine-d-amphetamine when it is unbound, namely, d-amphetamine"	
9(c)	"amphetamine as an active"	"the active amphetamine released from L-lysine-d-amphetamine, namely d-amphetamine"	
9(e)	"amphetamines" *and* "said amphetamine"	"the genus of amphetamines"	
9(f)	"an amphetamine"	"an amphetamine from the genus of amphetamines"	
9(g)	"released amphetamine" *or* "amphetamine released from the prodrug"	"the amphetamine released from L-lysine-d-amphetamine, namely d-amphetamine"	
9(h)	"The composition of claim 1 . . . to treat a patient in need of amphetamine"	"The composition of claim 1 … to treat a patient in need of the amphetamine released from the composition of claim 1"	
9(i)	"and having an amphetamine base amount"	"and having an amount of amphetamine component of L-lysine-d-amphetamine or a salt thereof, namely, d-amphetamine"	

The parties dispute whether the term "amphetamine" carries a different construction in different claim contexts. Norwich broadly construes the term to mean "any sympathomimetic phenethylamine derivative that has central nervous system stimulant activity" in all contexts. (ECF No. 77 at 27). Takeda, by contrast, does not apply an identical construction across all claims. (Taft ¶¶ 63-141). While Takeda's construction acknowledges that a broad construction of the term "amphetamine" is appropriate in certain contexts (*i.e.*, Terms 9(e)-(f)), for many claims, such a broad construction cannot be correct. In certain instances, the term "amphetamine" refers specifically to "d-amphetamine," such as that released from "L-lysine-d-amphetamine" (*i.e.*, Terms 9(a)-(d), (g)-(i)). Takeda's construction properly reflects the different claim contexts in which the term arises.

A single definition of a claim term does not universally apply if "it is clear from the specification and prosecution history that the terms have different meanings at different portions of the claims." *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.*, 442 F.3d 1322, 1328 (Fed. Cir. 2006). "Surrounding words" or "modifiers" of a claim term may "inform[] the interpretation" of the term and "produce significant differences" in construction. *Id.* "Extracting a single word from a claim divorced from the surrounding limitations can lead construction astray." *IGT*, 659 F.3d at 1117.

The patents-in-suit define "amphetamine" as both (i) a specific amphetamine molecule or (ii) a genus of amphetamine drugs. For example, the specification of the '486 patent uses the term "amphetamine" in different ways within the same sentence:

> "**Amphetamine**" shall mean any of the sympathomimetic phenethylamine derivatives which have central nervous stimulant activity, such as but not limited to, **amphetamine**, methamphetamine, . . . and 3,4-methylenedioxymethamphetamine.

(Ex. 1, '486 patent, col. 10 ll.13–19 (emphasis added); Taft ¶¶ 63-65). In the above passage, the first use of "amphetamine," in context, refers to a class of drugs, whereas the second use refers to specific amphetamine molecules. (Taft ¶ 64). Elsewhere, the patents-in-suit refer to specific amphetamine molecules by labeling the chemical structure as "Amphetamine." (*E.g.*, Ex. 2, '735 patent, col.10 ll.1–11). Further, the patents-in-suit use "amphetamine" as an abbreviation for a specific isomer, such as d-amphetamine. (*E.g.*, Ex. 9, '031 patent, Example 12, col.30 l.57 – col. 31 l.19). Likewise, the specifications explain that "Lysine-Amphetamine" is an abbreviation for L-lysine-d-amphetamine. (*E.g.*, Ex. 2, '735 patent, col.10 ll.12–17). Because the term "amphetamine" is used both broadly to refer to a class of drugs and narrowly to refer to a specific molecule, the claim context is necessary to determine the proper construction of the term.

In the Prior Litigation, this Court rejected a construction for certain terms set forth by plaintiffs in that action that was similar (though not identical) to Takeda's construction here. *Shire*, 2013 WL 4045622 at *8. Takeda respectfully submits that it is appropriate for the Court to deviate from its prior ruling. First, Takeda offers new terms and corresponding constructions in the instant litigation that are supported by intrinsic and extrinsic evidence. Second, this Court's construction in the Prior Litigation was based on the "broadest reasonable interpretation" of the claim, rather than the *Phillips* standard. *See Phillips*, 415 F.3d at 1313. *Phillips* instructs that a claim term must be given "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* Although in the Prior Litigation, the Court expressly recognized that "the patentees appeared to use 'amphetamine' in both broader and narrower ways," it adopted the broader construction, noting that "[i]n claim construction, the Federal Circuit gives claim language the broadest reasonable construction, in light of the specification." *Shire*, *LLC*, 2013 WL 4045622 at *8. Since then, the Federal Circuit has instructed that a prior construction based on

the broadest reasonable interpretation standard "cannot be dispositive" where the *Phillips* standard is to be properly applied. For example, in *Convolve, Inc. v. Compaq Computer Corp.*, the Federal Circuit held that a district court erred to the extent it "adopted [the broadest reasonable interpretation] wholesale without accounting for the differences between the broadest reasonable interpretation standard and *Phillips*." 812 F.3d 1313 (Fed. Cir. 2016). Finally, for certain claims, the prior *Markman* Order did in fact apply a narrow, rather than broad, construction of amphetamine for certain terms (as discussed below). It is appropriate to do the same here.

i. For Terms 9(a)-(d) and (g)-(i), "Amphetamine" Refers to "D-Amphetamine"

a. The Claim Language Arises in the Context of L-lysine-d-amphetamine

"Claim construction must begin and remain centered on the claim language." *Skedco, Inc. v. Strategic Operations, Inc.*, 685 Fed. App'x 956, 959 (Fed. Cir. 2017) (citing *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir. 2003)). With respect to terms 9(a)-(d) and (g)-(i), the claim language indicates that the "amphetamine" term ***cannot*** broadly refer to the genus of amphetamines, as required by Norwich's construction. Rather, as reflected by Takeda's construction, the claimed "amphetamine" term specifically refers to "d-amphetamine"—the same amphetamine as released from L-lysine-d-amphetamine.

The applicable claims for terms 9(a)-(d) and (g)-(i) do not refer to "amphetamine" in isolation, but instead make reference to the term in the context of a composition or prodrug comprising "L-lysine-d-amphetamine." A proper claim construction must account for this context. "While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim must also be considered in determining the ordinary and customary meaning of those terms." *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003);

accord Phillips, 415 F.3d at 1314 ("To begin with, the context in which a term is used in the asserted claim can be highly instructive.").

Dependent claim 5 of the '561 patent (term 9(g)) is illustrative. The claim recites "released amphetamine" from the "pharmaceutical composition of claim 1":

> 5. The pharmaceutical composition of claim 1, wherein the C_{max} of ***released amphetamine*** is within about 80% to about 120% of a value selected wherein said value is 53.2±9.62 ng/mL, 93.3±18.2 ng/mL, or 134±26.1 ng/mL.

(Ex. 15, '561 patent, claim 5). From claim 5, a POSA understands that the context of "released amphetamine" is dependent on the "pharmaceutical composition of claim 1." (Taft ¶ 122). As recited by claim 1, the claimed "pharmaceutical composition" comprises "L-lysine-d-amphetamine or a pharmaceutically acceptable salt thereof":

> 1. A pharmaceutical composition comprising: a. about 10 mg to about 250 mg of ***L-lysine-d-amphetamine*** or a pharmaceutically acceptable salt thereof; b. about 40% to about 90% by weight percent of microcrystalline cellulose; c. about 1% to about 10% by weight percent of croscarmellose sodium; and d. less than about 5% by weight percent of magnesium stearate.

(Ex. 15, '561 patent, claim 1). Accordingly, a POSA would understand that the "C_{max} of ***released amphetamine***" must refer to the C_{max} of amphetamine released from "L-lysine-d-amphetamine or a pharmaceutically acceptable salt thereof" included in the composition of claim 1. (Taft ¶ 122). A POSA would understand from the specification that the amphetamine released from L-lysine-d-amphetamine is not any amphetamine from the genus of amphetamines, but rather, is specifically "d-amphetamine." (*See*, *e.g.*, Ex. 15, '561 patent at col.10 ll.51-67; Taft ¶¶ 27, 122). Thus, the only reasonable interpretation of term 9(g) is Takeda's construction, d-amphetamine. (*See* Taft ¶¶ 118-126).

The same reasoning holds true for any disputed term that refers to "amphetamine" released from a specifically recited prodrug or composition comprising "L-lysine-d-amphetamine." Terms

9(c) and 9(i) both arise in this very context. For example, term 9(c) refers to "amphetamine as an active" released "***from said prodrug***." (Ex. 2, '735 patent at claims 1 and 18 (emphasis added); Taft ¶¶ 94-101). The referenced "prodrug" is a prodrug consisting of "L-lysine-d-amphetamine." Accordingly, the claims require the term "amphetamine as an active" to mean "the active amphetamine released from L-lysine-d-amphetamine, namely d-amphetamine."

Likewise, term 9(i) recites a milligram amount of L-lysine-d-amphetamine and a corresponding "amphetamine base amount . . . ***of said amphetamine***." (*E.g.*, Ex. 8, '030 patent at claim 1 (emphasis added)). The plain language of these claims indicates that "amphetamine base amount" refers to a component of "said amphetamine" (i.e., the base amount of the amphetamine component of L-lysine-d-amphetamine). (Taft ¶¶ 134-141). Thus, a POSA would have understood that the "amphetamine base amount" refers to the amount of the d-amphetamine component in L-lysine-d-amphetamine. Indeed, this Court adopted a narrow construction for term 9(i) in the Prior Litigation and rejected defendants' proposed construction whereby "amphetamine base" referred to "some other amount of amphetamine base" besides the d-amphetamine from L-lysine-d-amphetamine. *See Shire*, 2013 WL 4045622 at *10. In the Prior Litigation, "Plaintiffs contend[ed] that the base amount refers to the d-amphetamine component of LDX." *Id.* This Court agreed, finding that "[t]he amphetamine base amount is unambiguously some component of the 'said amphetamine,' as Plaintiffs contend." *Id.*

Analogously, term 9(h) refers to "[t]he composition of claim 1 . . . to treat a patient in need of amphetamine." (Ex. 2, '735 patent at claim 9; Taft ¶¶ 127-133). Based on the language of the claim, a POSA would not understand term 9(h) as referring to "a patient in need of" ***any*** amphetamine generally (e.g., methamphetamine), but rather, "a patient in need of the amphetamine released from the composition of claim 1." (Taft ¶¶ 128-130). Claim 1, in turn, recites "[a]

pharmaceutical composition comprising an unprotected prodrug . . . wherein said prodrug consists of L-lysine-d-amphetamine or a pharmaceutically acceptable salt thereof . . . wherein said composition provides release of amphetamine as an active ***from said prodrug*** . . . ." (Ex. 2, '735 patent at claim 9 (emphasis added)). Thus, a POSA understands that the composition of claim 1 releases the specific amphetamine "***from said prodrug***," i.e., from said composition comprising L-lysine-d-amphetamine. As set forth above, a POSA would understand the amphetamine released "from" L-lysine-d-amphetamine is d-amphetamine. Accordingly, a POSA would understand that claim 9 requires "a patient in need of amphetamine" to mean "a patient in need of the amphetamine released from the composition of claim 1," namely d-amphetamine.

Further, many of the disputed terms involve a comparison between (i) "amphetamine alone" (term 9(a)) or "unbound amphetamine" (terms 9(b), (d)) and (ii) a composition comprising "L-lysine-d-amphetamine." (*See* Taft ¶¶ 70-80, 81-93). A POSA understands that, when evaluating a prodrug's *in vivo* performance, the proper comparison is between the drug released from the prodrug and the drug itself (Taft ¶¶ 74-79, 95), and this understanding is borne out by the language of the claims. The claims do not refer to any "amphetamine" generally, but rather refer to "amphetamine ***alone***" or "***unbound*** amphetamine." A POSA would understand that "amphetamine alone" and "unbound amphetamine" refer to the "unbound" drug, or the drug "alone," which is the same as that released from the prodrug (i.e., d-amphetamine). (Taft ¶¶ 71-75, 82-90). Adopting Norwich's construction, which would allow the comparison to be between L-lysine-d-amphetamine and ***any*** amphetamine, would render the terms "alone" and "unbound" superfluous.

Because the language of terms 9(a)-(d) and (g)-(i) indicates that the referenced "amphetamine" term relates to the amphetamine that is released from L-lysine-d-amphetamine,

the full context of these claims supports Takeda's constructions wherein "amphetamine" means "d-amphetamine."

b. The Specification Confirms that the Amphetamine Released From L-lysine-d-amphetamine is Specifically D-amphetamine

Additionally, the specification—which is the "single best guide to the meaning of [a] disputed term" (*Phillips*, 415 F.3d at 1315)—confirms a POSA's understanding of the claims as set forth above. Based on the specification, a POSA understands that the term "amphetamine" is subject to a context-specific construction that may narrowly refer to the amphetamine released from L-lysine-d-amphetamine, namely d-amphetamine. (Taft ¶¶ 63-65, 68-69). For example, the specifications teach that the inventive prodrugs "provide[] covalent attachment of amphetamine . . . to a variety of chemical moieties . . . which results in a prodrug form, i.e., a molecule which is converted into its active form in the body by normal metabolic processes." (Ex. 2, '735 patent col. 3 ll. 40-47; *see also, e.g.*, Ex. 15, '561 patent col. 10 ll. 51-67 (teaching that "amphetamine is released from the chemical moiety by hydrolysis" upon oral administration); Taft ¶¶ 100, 124). Based on these disclosures, a POSA understands that, with respect to the inventive prodrug L-lysine-d-amphetamine, d-amphetamine is covalently attached to the chemical moiety L-lysine, which is converted into its active form, d-amphetamine, when exposed to normal metabolic processes. (Taft ¶ 100; *see also* Ex. 2, '735 patent col. 4 ll. 8-15).

The specification further teaches advantages of the inventive compounds that are directly related to the release of the active form of amphetamine (e.g., d-amphetamine) from the chemical moiety to which it is bound (e.g., L-lysine). Such advantages include (i) reduction in the "rate of absorption of the amphetamine as compared to delivering the unbound amphetamine" (Ex. 2, '735 patent col. 12 ll. 17-22), and (ii) "maximum release of the amphetamine . . . into circulation . . . over an extended period of time as compared to amphetamine alone" when delivered by oral route

(*id.* at col. 14 ll. 54-60). Thus, a POSA would understand the claims in relation to the benefits taught by the specification concerning the release of d-amphetamine from L-lysine-d-amphetamine. (Taft ¶ 78).

Moreover, the specification explicitly teaches that the "amphetamine base amount" in a composition comprising a certain amount of L-lysine-d-amphetamine is d-amphetamine. For example, the patents-in-suit include Table 2 as well as descriptions of Figures 61A and 61B, which describe the corresponding amounts of d-amphetamine in a salt of L-lysine-d-amphetamine. (*See* Ex. 8, '030 patent col.5 ll.34–39, col.18 ll.47–67; Taft ¶¶ 140-141). The specifications describe the amount of d-amphetamine base contained in L-lysine-d-amphetamine:

> [O]ral administration of L-lysine-d-amphetamine (25 mg L-lysine-d-amphetamine dimesylate containing 7.37 mg d-amphetamine base) to humans.

(Ex. 8, '030 patent col. 5 ll. 34-39; Ex. 10, '774 patent col. 5 ll. 34-39; Ex. 12, '771 patent col. 5 ll. 34-39; Ex. 14, '467 patent col. 5 ll. 34-39; Ex. 17, '619 patent col. 5 ll. 34-39; Ex. 18, '305 patent col. 5 ll. 34-39). As such, a POSA reading the claims in light of the specification would understand that with respect to terms 9(a)-(d) and (g)-(i), the claimed "amphetamine" term refers specifically to "d-amphetamine"—the same amphetamine released from L-lysine-d-amphetamine. (Taft ¶¶ 70- 101, 118-141).

i. For Terms 9(e)-(f), "Amphetamine" Refers to the Genus of Amphetamines Generally

In contrast to the claim terms described above, terms 9(e)-(f) refer generally to "the genus of amphetamines." Norwich's construction, which encompasses the genus of amphetamines, does not appear to dispute this. Nevertheless, it is worth highlighting terms 9(e)-(f) to understand that construction of the term "amphetamine" in the patents-in-suit is context- and claim-specific. Claim 1 of the '788 patent is exemplary of term 9(e) and recites:

> A method of decreasing abuse of **amphetamines** or salts thereof, in a subject in need thereof, said method comprising supplying **said amphetamine** to said subject in the form of L-lysine-d-amphetamine.

The claim language does not indicate that "abuse of amphetamines" relates to the amphetamine released from L-lysine-d-amphetamine; by contrast, the claim language suggests that supply of amphetamine "in the form" of L-lysine-d-amphetamine "decreas[es] abuse" of amphetamine ***not*** delivered in said form. (Taft ¶ 106). Thus, a POSA would understand from the claim language that while "amphetamines" generally may be subject to abuse, supply of "said amphetamine" in the "form of L-lysine-d-amphetamine" may decrease abuse. The specification supports the same. (Ex. 7, '788 patent Abstract, col. 1 ll. 51-53).

Finally, a POSA would understand term 9(f)—which includes the phrase "an amphetamine" and appears in the '788 patent, the '031 patent, and the '936 patent—as reciting methods of treating attention deficit hyperactivity disorder using "an amphetamine" in the form of L-lysine-d-amphetamine or a salt thereof. (Taft ¶¶ 110-117). Certainly, in the context of the claims, a POSA understands that "an amphetamine" is "an amphetamine" from the genus of amphetamines, within which L-lysine-d-amphetamine falls. (Taft ¶ 114).

E. Term 14: "Isolated" Refers to a Separated Substance

Term	*Takeda's Construction*	*Norwich's Construction*
"Isolated"	"a substance separated from a crude mixture of reactants and/or solvents"	"non-salt form"

In the Prior Litigation, all parties (including a defendant represented by Norwich's current counsel and executives) agreed to the construction that Takeda now proposes: "a substance separated from a crude mixture of reactants and/or solvents." (Ex. 46, TAKVYV01745249 at 254). This construction is consistent with the term's plain and ordinary meaning. (Chyall ¶¶ 53-65). By contrast, Norwich proposes a litigation-driven construction (i.e., "non-salt form")

designed to exclude Norwich's dimesylate salt ANDA product from the scope of the term. But the patents-in-suit do not define "isolated" as a "non-salt form," nor is this construction supported by the plain and ordinary meaning of the term. Takeda's construction should be adopted.

The relevant claims recite:

> 1. A compound selected from the group consisting of isolated L-lysine-d-amphetamine and a pharmaceutically acceptable salt of L-lysine-d-amphetamine.
>
> 2. Isolated L-lysine-d-amphetamine.

(Ex. 6, '787 patent claims 1, 2). The parties have agreed to a construction of the term "L-lysine-d-amphetamine." (*See* ECF No. 77 at 2). Thus, the only dispute concerns the meaning of the term "isolated."

Takeda's construction is consistent with the specification and examples of the patents-in-suit. For example, besides the claims, the ***only*** use of the word "isolated" in the specification occurs in the context of Example 2. Example 2 of the '787 patent describes the "synthesis of L-lysine-d-amphetamine." The synthesis involves two steps: (a) coupling and (b) deprotection. The term "isolated" appears in the "coupling" step. (*See* Ex. 6, '787 patent col. 20 l.64-col. 21 l.2) ("The crude product was dissolved in ethyl acetate and loaded on to a flash column . . . and eluted with ethyl acetate. The product was ***isolated***; the solvent reduced by rotary evaporation and the purified protected amide was dried by high-vac to obtain a white solid") (emphasis added)). A POSA would understand that the term "isolated" in the specification of the '787 patent refers to the separation of the product from a crude mixture using chromatography. (Chyall ¶ 55). This understanding is consistent with Takeda's construction.

Takeda's construction is further supported by the prosecution history of the '787 patent. The word "isolated" was added by an Examiner's Amendment on Sept. 20, 2009, where the Examiner was attempting to distinguish a hypothetical intermediary allegedly formed during the

synthesis of N-tosyl-L-lysine-d-amphetamine. (Ex. 24, TAKVYV01708913; Chyall ¶¶ 56-59). Thus, the term appears to have been inserted by the Examiner to avoid covering L-lysine-d-amphetamine which the Examiner implied could be hypothetically formed alongside reactants in the formation of another end product. While the applicants disagreed with the Examiner's analysis of the prior art, they nonetheless agreed to the addition of the word "isolated." (*See* Ex. 24, TAKVYV01708704 at 1715694; Chyall ¶¶ 56-59).

Additionally, the articles in the '787 file history use "isolated" in a similar manner as Takeda's construction to indicate the separation of a substance from a crude mixture of reactants and/or solvents. (*See*, *e.g.*, Ex 24, TAKVYV01708704 at 1708948 ("PepT1 has been isolated from various other species"); *id.* at 1709033 ("N-carboxy L-glutamic anhydride (Leuchs anhydride III) may be isolated from the reaction mixture"); *id.* at TAKVYV01709034 ("practically pure pyroglutaniic acid was isolated together with a small amount of glutamic acid"); *id.* at TAKVYV01709224 ("Three different products [] were identified, separated, and isolated"); *id.* at TAKVYV01709628 ("The resultant white precipitate was isolated by centrifugation"); *id.* at TAKVYV01709336 ("pure polymer was isolated from water solution by freeze drying"); and *id.* at TAKVYV01715276 ("The product was isolated by filtration washed with IMS 2 x 12m1 and dried in vacuo at 40 to 45°C to yield the title compound [a "hemisulfate salt"]"); *see also* Chyall ¶ 63). The file histories provide further intrinsic support for Takeda's construction. *See Kumar v. Ovonic Battery Co., Inc.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003) ("Our cases … establish that prior art cited in a patent or cited in the prosecution history of the patent constitutes intrinsic evidence.").

Extrinsic evidence also supports Takeda's definition. For example, Takeda's definition is consistent with dictionary definitions of the word, which define the term "isolate" as "to set apart or cut off from a group or whole." (*See* Ex. 42, TAKVYV01743210 at 214 (Am. Heritage Desk

Dictionary); Chyall ¶ 60). Additionally, district courts have recognized that the term "isolated" relates to purification, and not to the exclusion of salt forms. *See*, *e.g.*, *Cipla Ltd. v. Sunovion Pharms. Inc.*, No. CV 15-424-LPS, 2017 WL 2778352, at *6 (D. Del. June 27, 2017) (construing "pure and isolated" as "a tartrate salt that is substantially free of any impurities"); *Thermolife Int'l, LLC v. Hi-Tech Pharms., Inc.*, No. 1:15-CV-00892-ELR, 2019 WL 2354983, *3 (N.D. Ga. Mar. 18, 2019), *report and recommendation adopted*, No. 1:15-CV-00892-ELR, 2019 WL 3526369 (N.D. Ga. June 4, 2019) (construing "isolated . . .compound" as "a compound that has been separated, to at least some extent, from a natural or synthetic source"); *Synthon IP, Inc. v. Pfizer Inc.*, 446 F. Supp. 2d 497, 512 (E.D. Va. 2006) (construing "isolated form" as "the form of the compound of formula (3) that has been separated from the other components of the crude reaction mixture, except that some amount of impurities, including residual amounts of the other components of the crude reaction mixture, may remain following the act of separation"); *Mannatech, Inc. v. Glycobiotics Int'l, Inc.*, 513 F. Supp. 2d 754, 762 (N.D. Tex. 2007) (construing "isolated and purified" as "separated from other, unwanted substances"). Takeda's construction accords with intrinsic and extrinsic evidence, and should be adopted.

By contrast, Norwich asks the Court to construe the term as "non-salt form." But this is not a meaning of "isolated." Indeed, when the patentee intended to designate a "non-salt form" in the '787 patent specification, it used the term "freebase"—not "isolated"—to do so. (*See* Ex. 6, '787 patent at col. 20 ll. 52, 60; Chyall ¶ 64). Because the patentee knew how to specify a non-salt form and chose not to do so in the claims, Norwich's construction is improper.

F. Terms 16-20: The "Milligram" Terms Should be Given Their Plain and Ordinary Meaning

Term	*Takeda's Construction*	*Norwich's Construction*
"25 to 75 mg"	Plain and ordinary meaning	No construction needed; plain and ordinary meaning, i.e., "precisely 25 mg to precisely 75 mg"
"7.37 to 22.1 mg"	Plain and ordinary meaning	No construction needed; plain and ordinary meaning, i.e., "precisely 7.37 mg to precisely 22.1 mg"
"25 mg" / "75 mg"	Plain and ordinary meaning	No construction needed; plain and ordinary meaning, i.e., "precisely [25 mg / 75 mg]"
"30 mg / "50 mg" / "70 mg"	Plain and ordinary meaning	No construction needed; plain and ordinary meaning, i.e., "precisely [30 mg / 50 mg / 70 mg]"
"about 30 mg" / "about 50 mg" / "about 70 mg"	Plain and ordinary meaning	"approximately [30 mg / 50 mg / 70 mg]"

In the Prior Litigation, this Court ruled that certain "milligram" terms had their "plain and ordinary meaning." *Shire*, 2013 WL 4045622 at *11. It is appropriate for the Court to adopt the same construction as in the Prior Litigation, as proposed by Takeda here. (Chyall ¶¶ 66-78).

In the context of the patents-in-suit, numerical values are understood to have some flexibility. A POSA would have understood that the "milligram" terms refer to the strength of a dose. (Chyall ¶ 69). In other words, it refers to the amount of drug substance that a manufacturer claims is contained for each unit dose. (*Id.*). However, these terms do not refer to "precisely" the recited milligram amount. (*Id.* at ¶¶ 66-78). As it would have been understood by a POSA, there is some variability in the value of the dosage strength. The reason for such variability arises from the variability in the manufacturing processes used for the drug products. (*Id.*).

Likewise, a POSA would have understood claims reciting "about" a specified milligram value (i.e., '561 patent claims 2-4 (reciting "about 30 mg," "about 50 mg," and "about 70 mg," respectively)) in accordance with their plain and ordinary meaning. Such claims require "about" the specified milligram amount, and therefore, such claims contemplate variability in this value

that is greater than the variability associated with the recitation of the milligram amount alone. (Chyall ¶ 75).

Norwich—not Takeda—proposed this term for construction. Despite proposing the term for construction, the very first portion of Norwich's construction is "no construction necessary." Nevertheless, Norwich's construction inserts the word "precisely" into the definition—purporting that "precisely" is the plain and ordinary meaning of the term. [redacted] (*See, e.g.*, Ex. 49, NPILDX_000002746 at 747; Ex. 50, NPILDX_000002753 at 754; Ex. 51, NPILDX_000002760 at 761; Ex. 52, NPILDX_000002767 at 2768; Ex. 53, NPILDX_000002774 at 775; Ex. 54, NPILDX_000002781 at 782; Ex. 55, NPILDX_000002788 at 789; *see also* Chyall ¶ 74). [redacted] (Ex. 48, NPILDX_000000427 at 431-434; Ex. 58 (Norwich's Objections and Responses to Plaintiffs' First Set of Requests for Admission) [redacted]). [redacted] The Court should adopt its previous construction.

V. Conclusion

Because Takeda's constructions are aligned with the intrinsic evidence, extrinsic evidence, and the POSA's understanding of the terms, the Court should adopt Takeda's constructions.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of (i) Takeda's Opening Claim Construction Brief, (ii) Declaration of Dr. David R. Taft, Ph.D. in Support of Takeda's Opening Claim Construction Brief, (iii) Declaration of Dr. Leonard J. Chyall, Ph.D. in Support of Takeda's Opening Claim Construction Brief, and (iv) Declaration of Andrew S. Roper, Esq. in Support of Plaintiffs' Opening Claim Construction Brief (including Exhibits 1-58), was caused to be served on all counsel of record by email and ECF on July 27, 2021.

/s/ *Sylvia-Rebecca Gutiérrez*
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